REMARKS

In response to the Restriction Requirement, mailed March 24, 2004, Applicant elected with traverse, Group XXIV, claims 57-64, directed to nucleic acid molecules encoding Rep proteins. Applicant also elected for search purposes, with traverse, a single nucleic acid molecule also, encoding a mutant Rep protein where the mutation is a replacement of a T by N at position 350 in the Rep78 protein, the AAV serotype is AAV-2 and the mutant has increased activity as compared to the native protein.

Responsive to the communication, mailed December 15, 2004, Applicant now clarifies the election of species, with traverse, by specifying a SEQ ID NO. as requested by the communication. Applicant elects for search purposes, with traverse, SEQ ID NO:113. The Response and Amendment mailed July 6, 2004 is reproduced herein with the addition of this clarification. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 45, 46, 62, 70, 78, 94 and 95 are pending in this application. Claims 1-44, 47-61, 63-69, 71-77, 79-93 are cancelled herein without prejudice or disclaimer. Applicant reserves the right to file divisional applications to the cancelled subject matter

Claims 45 and 62 are amended herein. Claim 45 is written in independent form incorporating the limitations of 44. Claim 62 is amended to depend on claim 45 and additionally to incorporate the limitations of claims 6 and 12 on which it originally depended. These amendments find basis in the application as filed. Claim 45 finds basis, for example at page 28, lines 6-24. Claim 62 finds basis for example at pages 31-32.

Claims 94 and 95 are added herein. These claims find basis in the claims as filed. Claim 94 finds basis in original claims 7 and 57. Claim 95 finds basis in original claims 8 and 58. Claims 94 and 95 also find basis in the specification, for example at page 32, lines 3-17 and at pages 53-71.

Traversal of the Requirement for Restriction

Applicant traverses the Requirement for Restriction for the following reasons. Applicant respectfully submits that the Requirement for Restriction as currently drafted contains numerous errors. For example, the restriction requirement is incomplete because claims 12, 26-29 and 43 are not included. Further, without admitting that the Requirement as set forth is correct, it appears that claim 12 belongs in Group II, claims 26-29 belong in Group VIII and claim 43 belongs in Group XVIII. Since these claims are cancelled herein, most of these issues are rendered moot.

Applicant respectfully requests reconsideration of the restriction between claims 45-46, 62, 70 and 78. As discussed below, claim 45 is a linking claim, linking Group XVIII to Group XXIV. Further, each claim of Group XXV, claims 70 and 78, is related to Group XXIV as a subcombination/combination.

Linking Claim

Groups XVIII and XXIV

Groups XVIII and XXIV should be examined together because Group XVIII includes a linking claim. Pursuant to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on:

1) specifying the linking claims; and

2) examining the linking claims with the elected group. The linking claims must be examined with the elected group; if the linking claims are deemed allowable, then the restriction requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined.

In this case, Group XVIII includes claims linking it to group XXIV. Claim 45 of Group XVIII is directed to a nucleic acid molecule that encodes a mutant Rep with increased activity:

> 45. A nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity, wherein increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene.

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies particular amino acid replacements in the mutant Rep protein:

> 62. A nucleic acid molecule of claim 45, comprising mutations at one or more of residues, wherein the mutations comprise replacements of the native amino acid residue(s) selected from the group consisting of: T by N at position 350; T by I at position 462; P by R at position 497; P by L at position 497; P by Y at position 497; T by N at position 517; G by D at position 598; G by S at position 598; or V by P at position 600 of AAV-2 or the corresponding residues in other serotypes, wherein:
>
> residue 1 corresponds to residue 1 of the Rep78 protein encoded by nucleotides 321-323 of the AAV-2 genome; and
>
> whereby the activity of the mutant Rep protein is increased as assessed by rAAV production compared to the native Rep protein.

Comparison of claim 45 and claim 62 shows that claim 45 encompasses a nucleic acid molecule encoding a mutant Rep protein of increased activity where the increased activity is manifested as an increase in virus titer. Claim 62 is directed to a nucleic acid molecule of claim 45 that includes the specified amino acid replacements in the Rep protein. Thus, claim 45 is a genus of nucleic acid molecules encoding a mutant Rep protein with increased activity as assessed by increased AAV titer and claim 62 is directed to species of nucleic acid molecules encoding Rep protein with increased activity and which have the mutations as specified.

Thus, claim 45 and claim 62 are related as genus/species. Genus claims linking species claims are one example of linking claims. *See* MPEP §809.03. Thus, claim 45 is a linking claim. Since claim 45 is a linking claim, restriction between Groups XVIII and XXIV is not proper. As noted above, linking claims must be examined with the elected species claims. MPEP §809. Therefore, it is respectfully requested that since Group XVIII contains a linking claim (claim 45) to Group XXIV, these groups should be examined together.

Combination/Subcombination claims

Group XXV and Group XXIV

It is respectfully submitted that Group XXV (claims 70 and 78) should be examined with Group XXIV (claim 62) because the claims in these groups are related as a combination/subcombination. Claims that are related as a combination and subcombination are distinct and restriction may be proper only if it can be shown that the combination as claimed does not require the particulars of the subcombination as claimed for patentability and that the subcombination has utility by itself or in other combinations. *See* MPEP §806.05(c) which states:

> If there is no evidence that combination ABsp is patentable without the details of Bsp, restriction should not be required. Where the relationship between the claims is such that the separately claimed subcombination Bsp constitutes the essential distinguishing feature of the combination ABsp as claimed, the inventions are not distinct and a requirement for restriction must not be made, even though the subcombination has separate utility.

For example, claim 70 is directed to a recombinant rAAV comprising the nucleic acid molecule of claim 62. Thus, claim 70 is a combination of an rAAV and the nucleic acid molecule of claim 62 (the subcombination). Similarly, claim 78 is directed to a cell comprising the recombinant AAV of claim 70. Claim 78 is a combination of a cell comprising an rAAV and the nucleic acid molecule of claim 62. In this case, the combinations (the rAAV and cells of claims 70 and 78, respectively) require the particulars

of the subcombination (the nucleic acid molecule of 62) for patentability. *See* MPEP §806.05 (c). If the nucleic acid molecule of claim 62 is deemed novel and unobvious, then the rAAV and cell of claims 70 and 78 are necessarily novel and unobvious. Thus, the combination as claimed (claims 70 and 78) requires the particulars of the subcombination as claimed (claim 62) for patentability. Therefore, Group XXV (claims 70 and 78) should be examined with Group XXIV (claim 62).

If the claims are restricted into these two groups, applicant ultimately could be granted two patents, one that includes claims directed to the nucleic acid molecules of Group XXIV, and another with claims directed to rAAVs and cells of Group XXV containing the nucleic acid molecules, that expire on different dates. If the claims to the subcombination (Group XXIV) issued first, a later issuing patent encompassing the combination (claims Group XXV) could not be held to constitute obvious-type double patenting over the earlier issuing patent. *See* MPEP §806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See also MPEP §804.01, which states:

> 35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

As noted above, if the nucleic acid molecules of claim 62 are deemed free of the prior art, then the rAAVs and cells of claims 70 and 78, which contain the nucleic acid molecules of claim 62, will necessarily be free of the prior art. Since restriction between Group XXIV (claim 62) and Group XXV (claims 70 and 78) is improper, reconsideration and examination of these claims together is respectfully requested.

Election of Species Traversal

The Office Action sets forth an election of species in Group XXIV because each claim allegedly recites a different sequence. Although, as discussed below, Applicant disagrees with the election of species requirement, Applicant has endeavored to comply with the election of species. Applicant has elected for search purposes species of nucleic acid molecules encoding a mutant rep protein where the mutation is a replacement of a T by N at position 350 in the Rep78 protein, the AAV serotype is AAV-2 and the mutant has increased activity as compared to the native protein (SEQ NO:113).

Applicant respectfully submits however, that such election of species is improper. The claims are all directed to nucleic acid molecules encoding variants in the same protein which should be examined together. Applicant further submits that the election of species improperly restricts the claimed subject matter to a nucleotide sequence encoding a single variant per claim.

The claimed species are all mutations in the same Rep protein

The subject matter of the claims is directed to nucleic acid molecules encoding an AAV Rep protein and variants therein, and virus and cells containing such nucleic acid molecules. As set forth in MPEP §803.04, nucleotide sequences encoding the same protein will be examined together. In the instant case, all of the claimed nucleic acid molecules encode an AAV Rep protein. The mutations at the specified positions are all in the Rep protein. The types of mutation (insertion, deletion or replacement) are all mutations in the Rep protein. Thus, because the claimed mutations are all positions and types of mutations in the same protein, they should be examined together.

Restrictions to Single Nucleotide Sequences

Notwithstanding the above arguments, according to MPEP §803.04, claims drawn to nucleotide sequences encoding different proteins are deemed properly restrictable, although the Commissioner has decided *sua sponte* to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. MPEP §803.04 states:

> Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patently indistinct from the selected sequences will also be examined.

Applicant respectfully submits that nucleic acid molecules encoding the types of Rep proteins should also be examined together. As noted above, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.

The types of AAV Rep protein, Rep 78, Rep68, Rep52 and Rep 40, are all encompassed within overlapping nucleic acid sequences. As described in the specification, Rep 78 is encoded by nucleotides 321-2186, Rep 68 is encoded by nucleotides 321-1906, Rep 52 is encoded by nucleotides 993-2186, and Rep 40 is encoded by nucleotides 993-1906 and 228-2252 of AAV (see for example, at page 31). Thus, the sequence of nucleotides encoding Rep 78 encompasses the sequences of nucleotides encoding Rep 68, Rep 52 and Rep 40. Hence, a search of nucleic acid molecules encoding one type of Rep protein (*e.g.*, Rep 78) is the same search as for nucleic acid molecules encoding all of the Rep proteins.

Applicant also respectfully submits that nucleotide sequences encoding the different AAV serotypes, AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5 or AAV6, also should be examined together. These serotypes constitute only seven nucleotide sequences encoding AAV Rep protein. Hence, this number falls within the reasonable limit of independent and distinct nucleotide sequences that can be examined together.

In summary, Applicant respectfully submits that because the types of Rep proteins are encompassed in overlapping nucleotide sequences and because there are only seven AAV serotypes, the number of species falls within the reasonable number of sequences that can be examined together as set forth in the MPEP. Therefore, Applicant respectfully requests that the election of species with respect to types of Rep proteins and AAV serotypes be withdrawn and that these species are examined together.

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In view of the election, amendments and remarks herein, examination on the merits is respectfully requested.

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17109-003001/ 37851-912
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